REMARKS

1. Preliminary Remarks

a. Status of the Claims

Claims 31, 32, and 39-42 are pending in this application. Claims 31, 32, and 39-42 are amended. Applicant respectfully requests entry of the amendments and remarks made herein into the file history of the application. Upon entry of the amendments, claims 31, 32, and 39-42 will be pending and under active consideration.

b. Amendments to the Claims

Support for the amended claims can be found in the application as originally filed as shown in Table A.

Table A

Claim	Support
31	¶¶ 0043 and 0044
32	¶¶ 0043 and 0044
39	¶¶ 0043-045
40	¶¶ 0043-045
41	¶¶ 0043-045
42	¶¶ 0043-045

c. Priority

On page 4 of the Office Action, the Examiner denies Applicant's claim for the benefit of an earlier filing date, because Applicant allegedly has not complied with one or more conditions required under 35 U.S.C. §§ 119 or 120. Specifically, the Examiner asserts that written description support for SEQ ID NOs: 6527 and 15 is not readily found in any of the prior-filed applications of which Applicant claims priority. Applicant respectfully disagrees. For example, priority U.S. App. No. 10/707,147, filed on November 24, 2003 (the "Priority Application"), the benefit of which Applicant has claimed, discloses SEQ ID NOs: 303 and 169. These sequences are identical to instant SEQ ID NOs: 15 and 6527, respectively. Furthermore, paragraphs 0012-0015 and the claims of the Priority Application disclose nucleic acids having these sequences, as well as probes and vectors comprising the nucleic acids. Accordingly, the instantly claimed sequences are supported in the Priority Application in the manner required under 35 U.S.C. § 112. In view of the foregoing, Applicant respectfully submits that the priority date for the instant claims for purposes of examination is no later than **November 24, 2003**.

d. Amendments to the Specification

Paragraph 0032 is amended to incorporate by reference the substitute sequence listing submitted herewith. Paragraphs 0283-0286 and 0307 are amended to add sequence identifiers to the sequences listed in these paragraphs. Paragraph 0283 is also amended to correct typographical errors.

e. Objections to the Specification

On pages 2 and 3 of the Office Action, the Examiner objects to the specification for allegedly failing to comply with the requirements of 37 C.F.R. §§ 1.821-1.825. Specifically, the Examiner asserts that paragraphs 0283-0286 and 0307 of the specification contain sequences that are not identified with sequence identifiers. These paragraphs are amended to add the sequence identifiers required under 37 C.F.R. §§ 1.821-1.825. The substitute sequence listing submitted herewith includes the sequences that are associated with the added identifiers. In view of the foregoing, Applicant respectfully requests that the Examiner reconsider and withdraw the objection to the specification.

f. Claim Objections

On page 5 of the Office Action, the Examiner objects to claims 39 and 40 for being related to vectors comprising RNA. The Examiner asserts that it is unclear how a vector may comprise RNA, since a "vector" ordinarily consists entirely of DNA. Applicant respectfully submits that the preparation of a vector comprising RNA is well within the skill of one of ordinary skill. In view of the foregoing, Applicant respectfully requests that the Examiner reconsider and withdraw the objection to claims 39 and 40.

2. Patentability Remarks

a. 35 U.S.C. § 101

On pages 5-11, the Examiner rejects claims 31, 32, and 39-42 under 35 U.S.C. § 101 because the claimed subject matter allegedly is not supported by a credible asserted utility. The Examiner acknowledges at page 5 that the claimed subject matter satisfies the specific and substantial criteria of the utility requirement. Thus, the only remaining issue with respect to utility is whether the claimed subject matter meets the credible utility requirement.

Applicant submits that the Examiner has failed to show that one of ordinary skill would have a reason to doubt Applicant's assertion of credible utility based upon the preponderance of the evidence presented on the record.

> If the applicant has presented facts that support the reasoning used in asserting a utility, Office personnel must present countervailing facts and reasoning sufficient to establish that a person of ordinary skill would not believe the Applicant's assertion of utility. The initial evidentiary standard used during evaluation of this question is a preponderance of the evidence (i.e., the totality of facts and reasoning suggest that it is more likely than not that the statement of the applicant is false.

MPEP §2107.02 III (A) citing In re Brana 51F.3d. 1560 (Fed. Cir. 1995).

Specifically, the Examiner has not presented any evidence that the Applicant's algorithm would result in a false positive identification of the microRNA/target mRNA binding between SEQ ID NO: 15 and its target gene sequence of SERPINA3. As presented previously, Dr. Pilpel declared that SEQ ID

NO: 15 and its target gene sequence of SERPINA3 are consistent with miRNA and target mRNA binding as predicted by known algorithms (citing TargetScan developed by Lewis *et al., Cell* 15:787-798 (2003) and miRanda developed by Enright *et al., Genome Biology* 5:R1 (2003)). Countervailing to the declaration, the Examiner argues that these comparative algorithms have a high level of false positive/negative rates between 22 and 39% (cites Bentwich et al., FEBS Letters 579:5904-5910 (2005) and Martin et al., J. Biosci. 32:1049-1052 (2007)). Applicant's response is that although the false positive/negative rates are between 22 and 39%, these same comparative algorithms successfully predicted miR/target gene interactions 61%-78% of the time. A 61-78% success rate in predicting an mRNA target gene for a miR would suggest to one of skill in the art that it is more likely than not (more than 50%) that the Applicant's assertion of utility is true.

Countervailing to the declaration, the Examiner also asserts that it is difficult to estimate true false positive/negative rates of miRNA prediction programs because few validated miRNA targets are known and a comparison of miRNA prediction efficiencies is not currently possible. The Examiner further asserts that multiple factors are involved in miRNA/target binding (citing Smalheiser *et al., Methods of Mol. Biol.* 342:115-127 (2006)). The Examiner's countervailing statement does not address any of the specific failings of the Applicant's algorithm or assertion that the miRNA/targeting pairing of SEQ ID NO: 15/SERPINA3 are inconsistent with known algorithms and therefore does not provide any weight to the evaluation process for utility. Again, because the Dr. Pilpel declared that SEQ ID NO: 15 and its target gene sequence of SERPINA3 are consistent with microRNA and target mRNA binding as predicted by known algorithms and these same comparative algorithms successfully predicted miR/target gene interactions 61%-78% of the time, one of ordinary skill in the art would more likely than not (more than 50%) that the Applicant's assertion of utility is true. In view of the foregoing remarks and presented evidence, Applicant submits that the rejection of claims 31, 32, and 39-42 under 35 U.S.C. §101 for lacking credible utility has been overcome and should be withdrawn.

b. 35 U.S.C. § 102

(1) Over Croce

On pages 12-15 of the Office Action, the Examiner rejects claims 40 and 42 under 35 U.S.C. § 102(e) as allegedly being anticipated by Croce *et al.* (U.S. Pat. Pub. No. 20060105360A1). Based on the priority date, as described in the remarks above, the effective filing date of the instant claims is no later than **November 24, 2003**. The § 102(e) date for Croce is **September 2, 2004**, and thus postdates the instant claims. Accordingly, Croce is not prior art. In view of the foregoing, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 102(e) over Croce.

(2) Over Venter

On pages 15 and 16 of the Office Action, the Examiner rejects claim 39 under 35 U.S.C. § 102(e) as allegedly being anticipated by Venter *et al.* (U.S. Pat. No. 6,812,339). The Examiner asserts that Venter teaches a vector comprising a nucleic acid sequence comprising instant SEQ ID NO: 6527.

The vector of amended claim 39 comprises a 131 nucleotide-long human insert. The vector does not contain any other human insert. However, the sequence taught by Venter is 346,112 nucleotides long, and therefore does not meet the length limitation of the insert of claim 39. Accordingly, Venter does not teach or suggest the subject matter of claim 39. In view of the foregoing amendment and remarks, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 102 over Venter.

(3) Over Zhao

On pages 16 and 17 of the Office Action, the Examiner rejects claim 40 under 35 U.S.C. § 102(b) as allegedly being anticipated by Zhao *et al.* (1997) GenBank Accession No. AQ420078. The Examiner asserts that Zhao teaches an isolated 684 nucleotide-long DNA sequence and BAC clone thereof comprising a sequence complementary to SEQ ID NO: 15. The Examiner further asserts that this BAC clone anticipates the vector of claim 40.

The vector of amended claim 40 comprises a 22 nucleotide-long human insert. The vector does not contain any other human insert. However, the insert taught by Zhao is 684 nucleotides in length, and therefore does not meet the length limitation of the insert of claim 40. Accordingly, Zhao does not teach or suggest the subject matter of claim 40. In view of the foregoing amendments and remarks, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 102 over Zhao.

c. 35 U.S.C. § 103

(1) Over Venter in view of Buck

On pages 17-20 of the Office Action, the Examiner rejects claim 41 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Venter as applied to claim 39 and further in view of Buck *et al.* (Biotechniques, 1999;27(3):526-38). The Examiner contends that because selection of primers yields predictable results, and because primers and probes would be expected to successfully bind to their targets according to the same principles as sequencing primers, it would have *prima facie* obvious at the time of the invention to make and use nucleic acid probes of **essentially any length** against **essentially any region** of the Venter sequence with anticipated success of detecting and or amplifying the corresponding regions in the Venter sequence. *Office Action*, at p. 18. Accordingly, the Examiner asserts that the probe of claim 41 is obvious in light of a genus of probes and primers taught by the cited art. Applicant respectfully disagrees.

Applicant submits that even if the probes and primers cited by the Examiner include the probe of claim 41, this is not sufficient by itself to establish a *prima facie* case of obviousness. *See MPEP* § 2144.08.II.A ("The fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness"). The group of probes and primers cited by the Examiner encompasses millions upon millions of different sequences. The claimed probe is but one subgenus within this massive genus of probes and primers. There is no teaching in either Venter or Buck to lead one of skill to select a probe or primer that is capable of specifically detecting a miRNA precursor sequence, or a miRNA sequence capable of regulating a gene transcript in *trans*, as is provided in claim 41.

To find a subgenus of sequences obvious in view of a genus of sequences the Examiner must show that it would have been obvious to one of skill to **select the claimed subgenus from the disclosed prior art genus**. *See Id.* Such a showing must be based on the evidence as a whole, and includes a consideration of (i) the size of the prior art genus; (ii) whether the prior art expressly teaches a particular reason to select the claimed subgenus; and (iii) whether the prior art teaches a typical, preferred, or optimum subgenus sequence within the disclosed genus. *See Id.*

(a) The probe of claim 41 is nonobvious in view of the massive size of the cited genus

Rejection of a claimed subgenus in light of a prior art genus is not appropriate where the prior art does not disclose a small recognizable class of species or subgenus with common properties. *See MPEP* § 2144.08.II.A.4(b). Given that the Venter sequence is **346,112** nucleotides in length, and that the Venter probes and primers can be of any length and recognize any region of the Venter sequence, the following illustration shows how an essentially innumerable genus of nucleic acids is capable of detecting this sequence based on the criteria of Buck. For the sake of argument, assume Buck teaches a lower length limit for a probe of 18 nucleotides and the instantly claimed probe insert provides an upper length limit of 131. The number of 18-mers capable of binding to the Venter sequence with 100% complementarity is **346,095**. Extending the length to a range between 18 and 131 nucleotides increases this number to **39,448,389**. The number of nucleic acids only increases when accounting for the Examiner's assertion that Venter teaches that an oligonucleotide typically "hybridizes under stringent conditions." According to Venter, hybridization under stringent conditions can be accomplished with nucleic acids that are at least about 60% homologous to each other. *Venter*, at col. 10, ln. 13. Allowing for 60% identity, the genus of no fewer than 39,448,389 nucleic acids grows exponentially. Therefore, rather than disclosing a small recognizable class of species or subgenus with common properties, Venter discloses a massive genus of probes and primer sequences, any of which could be used to detect the Venter sequence.

(b) There is no express teaching in the cited references to select the probe of claim 41

When a prior art reference teaches a particular reason to select the claimed subgenus, the Examiner must explain "why it would have been obvious to one of ordinary skilled in the art to select the claimed invention." *See MPEP* § 2144.08.II.A.4(b). Neither cited reference discloses a probe or primer that is designed to specifically detect a miRNA precursor sequence, or a miRNA sequence capable of regulating a gene transcript in *trans*. The Examiner acknowledges that Venter does not "expressly teach probes and primers comprising instant SEQ ID NO: 6527 or its complement." *Office Action*, at p. 18. Neither does Buck. Furthermore, the Examiner has failed to give any reason why one of skill would select SEQ ID NO: 6527 for use in the probe of claim 41.

(c) There is no teaching in the cited references of a "typical," "preferred," or "optimum" subgenus within the cited genus

A teaching in the prior art of a "typical," "preferred," or "optimum" subgenus within a disclosed genus, when the subgenus is structurally similar to that claimed, the disclosure may provide a reason for one of ordinary skill in the art to choose the claimed subgenus from the genus based on the reasonable expectation that the structurally similar species usually have similar properties. *See MPEP* § 2144.08.II.A.4(c). However, as discussed above, the Examiner asserts that Venter in view of Buck teaches that a nucleic acid used to detect the Venter sequence could be of **any length** and be directed to **any region** of the Venter sequence. *See Office Action*, at p. 18. Neither Venter nor Buck teaches a typical or preferred subgenus. The cited references do not teach that the probes or primers are useful for specifically binding to a miRNA precursor sequence having SEQ ID NO: 6527 or its complement. Further, Venter and Buck do not teach the desirability of a probe or primer with this property, or any property or utility, for that matter, that would lead one of skill to select the probe of instant claim 41 from the millions upon millions of primers and probes that they teach.

In fact, Venter teaches that its probes are specifically useful for detecting SNPs–not miRNAs. *See Venter*, at col. 8. Nowhere does Venter teach that SEQ ID NO: 6527 contains a SNP. Accordingly, Applicant submits that if Venter teaches any preference of probe or primer, the probe or primer should be designed to specifically detect a SNP, not miRNA precursor sequences or miRNA sequences capable of regulating gene transcripts in *trans*. Venter thus teaches a subgenus of probe or primer that would not include the insert of claim 41. Accordingly, Venter provides no structural relationship between the genus of Venter and the probe of claim 41 that would provide any motivation or suggestion to one of skill to arrive at the probe of claim 41.

In view of the totality of the circumstances, Applicant submits that there is no teaching in the cited references sufficient to establish that it would have been obvious to one of skill to select the probe of claim 41 from the genus of nucleic acids taught by Venter in view of Buck. The genus of sequences

taught by Venter is simply too massive, and there is no teaching of Venter or Buck–either expressly or through disclosure of a preferred form–that is sufficient to motivate one of skill to contemplate making the probe of claim 41. In view of the foregoing, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claim 41 under 35 U.S.C. § 103.

d. Remarks on prior art made of record but not currently relied on

On pages 20 and 21 of the Office Action, Lagos-Quintana *et al.* (2002) and Kim *et al.* (2004) were made of record but not relied upon by the Examiner. Accordingly, no comment on the statements made by the Examiner with respect to this reference is necessary.

3. Conclusion

Applicant respectfully submits that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

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Dated: September 30, 2008

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